

POST-REIMBURSEMENT FOLLOW-UP STUDY OF THE IMPLANTABLE AND RECHARGEABLE NEUROSTIMULATOR PRECISION®

Protocol

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BOSTON SCIENTIFIC

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SUMMARY

1	Synopsis	2
2	Background information	4
2.1	Spinal cord stimulation for analgesic purposes	4
2.2	The PRECISION® neurostimulator	4
2.3	Description of the centers involved in this therapy	5
2.4	Conditions for renewal of registration on the List of Products and Services	6
3	Objectives and endpoints	7
3.1	Objectives of the project	7
3.2	Endpoints.....	Erreur ! Signet non défini.
4	Methodology.....	8
4.1	Type of study	8
4.2	Study population	8
4.3	Data collection.....	9
5	Logistical aspects	13
5.1	Conduct of the study	13
5.2	Monitoring and data management	14
5.3	Study schedule.....	15
6	Analyses and reports.....	16
6.1	Analyses	16
6.2	Reports	18
6.3	Communication and publication	18
7	Bias and limits.....	19
7.1	Representativeness of the sample of investigators and patients	19
7.2	Difficulties in patient follow-up	19
7.3	No control cohort	20
8	Regulatory aspects	21
8.1	Sponsor of the study	21
8.2	Study funder	21
8.3	Scientific Committee	21
8.4	Administrative declarations	22
8.5	Material vigilance and post-marketing surveillance	23
8.6	Recommendation of good practices	23
8.7	Archiving	23
	Appendices.....	24
8.8	Appendix 1. Cerfa form (N°10246*04)	24
	Appendix 2. References.....	26

1 Synopsis

1. Title of the study	Post-reimbursement follow-up study of the implantable, rechargeable, spinal cord neurostimulator PRECISION®.
2. Number - version date	Version 10.2 - June 07, 2013
3. Sponsor	CEMKA-EVAL
4. Origin	Study carried out at the request of the High Authority of Health.
5. Centers / Investigators	All centers using the device over the inclusion period. These centers will be described for the criteria of geographical location, public or private status, volume of activity and specialities of the investigators. Doctors in these centers (neurosurgeons or anesthesiologists).
6. Population / Treatment studied	All patients implanted (primary implantation and replacement of device) with the PRECISION® neurostimulator during the inclusion period (1 year).
7. Objectives of the project	Evaluate the long-term effectiveness, complications, revision and final explant rates of the devices.
8. Evaluation criteria	<p>Primary Criterion: Percentage of patients with at least a 50% improvement in mean overall pain over the past 8 days, assessed by numerical scale, at the first follow-up visit, at 1 year and 2 years.</p> <p>Secondary criteria:</p> <ul style="list-style-type: none"> • Percentage of patients with an improvement of at least 30% in mean overall pain over the past 8 days, assessed by numerical scale • Patients' opinions on the evolution of pain • Evolution of consumption of other pain treatments (drugs and other therapies) • Evolution of the impact on activities of daily living • Evolution of quality of life (SF12), anxiety and depression (HAD questionnaire) • Explanation, reoperation or device change rate • Complications rate
9. Experimental plan	<p>Methodology: Prospective observational study with a 2-year follow-up</p> <p>Investigator Recruitment: Selected centers will be notified by mail. An implementation during on-site visits will be organized.</p> <p>Patient recruitment: During the inclusion period, the investigating centers should offer to participate in the study to all patients who have a spinal cord stimulator implant.</p>
10. Sample size	<p>Comprehensive study: the number of patients expected is estimated at about 100 patients over one year, corresponding to about 70 primary (first implanted) and 30 replacement of device patients.</p> <p>With a lost to follow-up of < 20%, this number makes it possible to estimate the main judgment criterion with an accuracy of $\pm 12\%$.</p>

11. Eligibility criteria	<p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Adult patient with a PRECISION® neurostimulator implanted in the spinal cord as a primary implant or in the replacement of their pacemaker. <p><u>Criteria for non-inclusion:</u></p> <ul style="list-style-type: none"> • Patient Refusal • Patient whose long-term follow-up will not be possible
12. Statistical method	<p>Statistical analyses will be carried out each year on the data collected.</p> <p>Data management and statistical analysis will be performed using SAS® software (North Carolina, USA). The descriptive analysis of qualitative and ordinal variables will include the number and frequency of each modality with its 95% confidence interval. The quantitative variables will include the mean, standard deviation and their confidence interval as well as the median and extreme values.</p> <p>For longitudinal analyses, survival analysis and mixed model analyses will take into account the follow-up time of each patient, the number of people lost to follow-up and missing data.</p>
13. Data collected	<ul style="list-style-type: none"> • <u>Inclusion data:</u> socio-demographic data (age, sex), indication of spinal cord stimulation, pain intensity and location, previous pain treatments, history), implantation data, early complications. • <u>Follow-up data</u> (follow-up at 1-3 months, 6 months, 1 year, 2 years): pain intensity (on a numerical scale), changes in drug use, complications, explant, revision. • <u>Patient data (self-questionnaire):</u> patient satisfaction, adverse events.
14. Duration of the study and estimated timetable	<ul style="list-style-type: none"> • <u>Total duration of the study:</u> 3.5 years (1 year of inclusion and 2 years of follow-up + analysis time) <ul style="list-style-type: none"> • Preparation of the study (protocol, questionnaires, regulatory affairs): 2011-2013 • Implementation in the centers: 2013 • Start Inclusion of patients: 2013 • End of patient follow-up: 2016 • Data management and data entry: Continuous • Analysis and report: Inclusion report: early 2015. 1-year follow-up report: early 2016. Final report: end of 2016.
15. Regulatory approaches	<ul style="list-style-type: none"> • Study not included in the scope of Biomedical Research (ex Huriet Law). • Request for authorization from CCTIRS and CNIL

2 *Background information*

2.1 Spinal cord stimulation for analgesic purposes

Spinal cord neurostimulation for analgesic purposes is a therapy developed over the past forty years. It is considered an effective (i-iv) alternative to repeated back surgery, drugs or other therapies, without causing damage to the nervous system: the complications related to the constituent materials of the components are few and generally benign.

The indications for spinal cord neurostimulation are as follows:

- irreducible chronic neuropathic pain, after failure of other therapeutic means, secondary to:
 - o chronic radiculalgia (sciatica, cruralgia, cervical-brachialgia)
 - o peripheral nerve damage, post-traumatic or post-surgical nerve damage
 - o amputation (algo-hallucinosi)
 - o a complex regional painful syndrome (sympathetic reflex dystrophies, peripheral causalgia)
- peripheral ischemic pain such as stage III, IV arteritis

Other therapeutic methods that should have previously been used include level I and II analgesics, physiotherapy, muscle relaxants, nerve block anaesthesia, antiepileptics, tricyclic antidepressants, transcutaneous neurostimulation coupled with physiotherapy and behavioural approach and, in the case of Burger's disease, prostacyclin.

2.2 The PRECISION® neurostimulator

Boston Scientific manufactures and markets in France an implantable and rechargeable spinal cord neurostimulator, PRECISION®. This device was the subject of two publications on non-comparative studies, respectively on 49 implanted patients (IDE study) 5 and 12 patients ineligible according to IDE and implanted study criteria (v).

The PRECISION® neurostimulator was the subject of a CEPP notice dated May 26, 2009 and a three-year registration on the List of Products and Services (Order of February 2, 2010, published in the Official Journal of February 10, 2010).

The information used by the CNEDIMTS

In the case of a rechargeable neurostimulator, PRECISION® is indicated for patients with the general indications of a spinal cord neurostimulation and requiring a high level of stimulation, resulting in:

- a lifetime of less than 30 months after the first implantation of a non-rechargeable implantable spinal cord neurostimulator
- or a stimulation threshold greater than 3.5 volts or 4.7 mA at the end of the test stimulation phase in naïve patients.

Terms of use and prescription

This system requires multidisciplinary medical care:

- In the context of a chronic pain management structure, for the validation of the indication, the evaluation of the results of the test stimulation and post-implantation follow-up;
- Implant of the system by a different person, trained in this type of action.

Long-term follow-up within the chronic pain management structure should be carried out to allow adaptation of stimulation parameters, drug treatments and to verify the achievement of pain reduction objectives.

The validation of the indication implies:

- An assessment of the various bio-psycho-social factors that may influence the patient's condition and may justify exclusion,
- The patient's adherence to the objectives of the treatment,
- Controls of the organic conditions allowing the installation of the device, in particular the satisfactory integrity of the posterior cords (Satisfactory Somesthetic Evoked Potentials),
- The performance of an epidural stimulation test prior to final implantation, for a minimum duration of 10 days with a desired "return home", with outpatient medical care for patients. The improvement in pain must be at least 50%.

Target population

In the CEPP opinion, the target population is estimated at between 82 and 165 patients per year.

2.3 Description of the centers involved in this therapy

Characteristics of the centers

As this is a newly marketed device, the number of centers performing the activity of placing PRECISION® analgesic neurostimulators is still in the ascending phase. According to information provided by Boston Scientific, there are approximately 15 centers in 2012.

According to Boston Scientific statistics, approximately 25 to 30% of the implants performed each year are for patients already implanted previously (replacement).

Patient follow-up

Patient follow-up is not really codified. Reprogramming or adjustment consultations are not subject to a specific quotation.

2.4 Conditions for renewal of registration on the List of Products and Services

The commission asks that the manufacturer set up "a register analyzing all implanted patients, including long-term effectiveness, complications, revision rates and final explant of the system".

The results of this study should be submitted to CEPP for review once a year. Renewal will be subject to the submission of the full results of the study.

In response to CEPP's request, Boston Scientific asked Cemka-Eval to set up an observatory for the first year of use of the device, with a 2-year follow-up of implanted patients.

3 Objectives and endpoints

3.1 Objectives of the project

In accordance with the request of the CNEDIMTS, the objectives of this post-reimbursement follow-up study are to evaluate the long-term efficacy, complications, revision and explant rates of the Boston Scientific rechargeable neurostimulator, PRECISION®.

3.2 Endpoints

The study of effectiveness in real practice will be based primarily on the **primary endpoint**, which is the percentage of patients improved by at least 50% on the numerical scale between the pre-implantation period and the measurements made during follow-up. This criterion will be assessed at the first follow-up visit, at 1 and 2 years. However, it can only be evaluated in primary implanted patients. To be as compatible as possible with the practice of collecting pain information in the centers concerned, it was decided to use a measure of the average overall pain over the last 8 days without distinction of location, using a numerical scale.

Pain measurements will also include questions on the level of pain present at the time of measurement and the level of the most intense pain over the past 8 days. These criteria will be used as secondary criteria.

Other **secondary judgment criteria** will be collected (or calculated) and analyzed:

- Percentage of patients improved by at least 30% on the numerical scale between the pre-implantation period and measurements made during follow-up, this criterion can be considered satisfactory and associated with a decrease in other treatments for some patients with neuropathic pain;
- Patients' views on pain relief;
- Evolution of the consumption of other pain treatments (drugs and other therapies);
- Evolution of the impact on activities of daily living, return to employment for working-age patients.
- Evolution of quality of life (measured on SF12), evolution of anxiety and depression measured on the HAD (Hospital Anxiety and Depression Scale) questionnaire.

Complication, revision and final explant rates will be calculated at each follow-up point based on the data available for the patients being monitored. The nature of the complications will be described in detail for each patient.

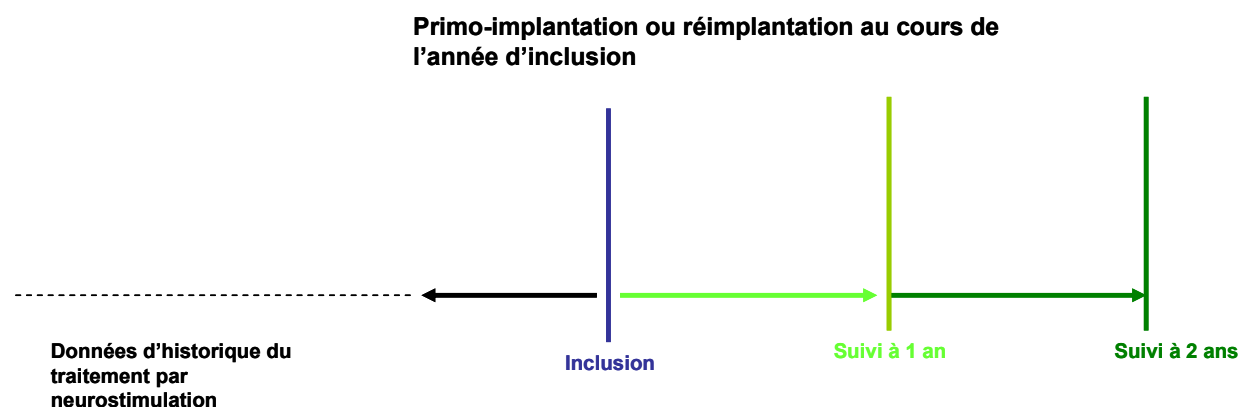
4 Methodology

4.1 Type of study

The principle adopted is that of a prospective study with a follow-up of patients for 2 years. Inclusion data will include a minimum of retrospective data to describe the patients implanted and in particular the implantation history of neurostimulators for analgesic purposes, particularly for patients in whom it is a stimulator replacement.

Follow-up questionnaires will be completed at 1 to 3 months, 6 months, 1 year and 2 years. **They will be completed during visits as part of the usual patient follow-up.**

Figure 1: Study design



4.2 Study population

Selection of centers

The study will cover all centers implanting PRECISION® neurostimulators in France. If new centers implement PRECISION® devices during the inclusion period, they will be included as they are implemented.

Criteria for patient inclusion

- All patients 18 years of age or older implanted with a PRECISION® neurostimulator during the inclusion period, including:
 - Naive patients (first implantation);
 - Patients previously implanted with a spinal cord stimulator, regardless of brand, and benefiting from the reimplantation of a PRECISION® neurostimulator (reimplantation).
- Patients who have read the newsletter and given their written consent.

For naive patients, the inclusion date will be the date of final implantation of the neurostimulator.

The inclusion period is set at 1 year. However, the Scientific Committee reserves the right to extend the inclusion period to include 100 first-time implant patients.

Exclusion criteria

- Patient Refusal
- Patient whose regular follow-up is difficult (patients living abroad and coming to France only for implantation)

For all these patients, the investigator will complete a non-inclusion register containing only the date of implantation of the PRECISION® neurostimulator and the reasons for non-inclusion (forgetfulness/lack of time, patient refusal, inability to consider long-term follow-up in the center).

Number of topics expected

This is a comprehensive one-year study. The PRECISION® neurostimulator having been recently marketed, it is still in a period of increasing load. The number of patients to be implanted in 2013 is estimated at 100 patients.

For the primary endpoint, which is the percentage of patients with pain improved by at least 50% (in primary implants), this percentage will be estimated with an accuracy of $\pm 12\%$, with the assumption of a percentage of 70% of primary implants in the cohort and the most negative assumption (in terms of accuracy) of 50% of improved patients.

4.3 Data collection

Data collection mode

The data collected will be of two kinds: data on pain characteristics and medical data. These will be collected by the doctor via an observation booklet composed of:

- 1 implant sheet,
- follow-up sheets identical to 1-3 months, 6 months, 1 year and 2 years,
- complication sheets, which can be completed at any time during follow-up if a complication occurs and several times for the same patient, if necessary.

To complete some elements of the questionnaire, the physician will have to interview the patient directly: For the measurement of pain intensity: he will ask the patient to be on the numerical scale and report the figure read on the scale on the questionnaire. For the degree of satisfaction, he will ask the patient and postpone his answer.

In addition, if the patient has not been seen in consultation during the first or second year, the CRA responsible for follow-up of the study will call the patient or his or her treating physician to collect news about at least the vital status and maintenance of the device.

The doctor must send the completed forms to the analysis center (Cemka-Eval) by T envelope. He or she will keep the original of the questionnaire in a patient follow-up binder.

In each center, patients will be included in the consecutive order of implantation, after informing the patient and subject to written consent (see Patient Information Letter).

An implant visit is planned, allowing the explanation of the study and the submission of data collection and patient information documents. Then, the follow-up of the centers will be done by telephone, email and summary and follow-up letters.

Data collected

The first page of the observation booklet contains the patient's date and place of birth, as well as his telephone number and the contact details of the patient's attending physician. This data will not be entered and will only be used if the patient is lost to follow-up before the end of the study. This page will therefore be detached from the questionnaire by the CRA of Cemka-Eval before the notebooks are entered.

The data collected will be as follows (see Observation Booklet):

Data at the time of implant:

- Sociodemographic data: year of birth, sex, professional activity (type, in activity, work stoppage, work accident, dispute);
- Characteristics of the pathology: seniority, significant history (surgical procedures, trauma), indications, pain topography, pain intensity, pain characteristics described by the DN4 questionnaire^{vi};
- Consumption of analgesic treatments (drugs and other therapies);
- Impact on activities of daily living;
- Quality of life (SF12);
- Type of pacemaker replaced and/or implanted and electrodes used; test before implantation;
- Parameters of the most effective stimulation (number of electrodes, number of active pads, pulse width, intensity, frequency, number of zones, material description).

Non-inclusion register :

A non-inclusion register will also be completed (see Non-inclusion Register), for all patients who meet the inclusion criteria but are not included. It will include the reason for non-inclusion.

Data at the time of follow-up visits:

- BPI (Brain Brief Pain Inventory) Questionnaire;
- Pain intensity (on the numerical scale);
- Patients' opinions on the evolution of pain
- Consumption of analgesic treatments (drugs and other therapies) and changes in relation to pre-implantation consumption;
- Impact on activities of daily living (concise pain questionnaire);
- Quality of life (SF12);
- HAD (Hospital Anxiety Depression Scale) Questionnaire;
- Professional situation, in order to document the returns to employment;
- Parameters of the most effective stimulation;

- For patients who have not been seen, the investigating physicians will be responsible for contacting the physician or family again to collect some of the information;
- Complications, if any, including explants or repositionings;
- If there is no follow-up in one of the 2 years, the CRA of Cemka-Eval will contact the patient or his attending physician to inform the part provided for this purpose in the follow-up questionnaires.

Complications data:

- The type of complication: electrode displacement/migration, pacemaker migration, electrode fracture, extension fracture, connector problem, skin erosion (healing phase or remote), epidural hematoma, infection, undesirable stimulation, allergy, exhausted battery, loss of efficiency and death...
- Hospitalizations or hospitalization extensions related to complications;
- Corrective actions to be taken following complications such as: electrode or extension change, electrode repositioning, pacemaker pocket revision, pacemaker change, pacemaker reprogramming (in case of loss of efficiency), explant.

Table 1: Summary of visits and data collected in the study

Visit number	0	1	2	3	4
	Inclusion	1-3 months	6 months (± 1 month)	12 months (± 1 month)	24 months (± 1 month)
Inclusion criteria	X				
Newsletter and patient consent	X				
Demographic characteristics	X				
Pain characteristics (physician data)	X				
Treatment history (doctor data)	X				
Pain characteristics (patient data)	X	X	X	X	X
Pain sensation (patient data)	X	X	X	X	X
Stimulation parameters	X	X	X	X	X
Treatments (patient data)	X	X	X	X	X
Pre-implantation test	X				
Implant	X				
Tolerance	X	X	X	X	X

Identification of adverse events

Adverse events will be collected as part of the complications collected in this observational study.

- Adverse events will be collected at inclusion visits, No. 1 follow-up at 1-3 months (±1 month), No. 2 follow-up at 6 months (±1 month), No. 3 follow-up at 12 months (±1 month) and No. 4 at end of study at 24 months (±1 month);
- Serious adverse events will be collected at any time during the study: from the inclusion visit and throughout the follow-up period.

NB: This data collection as part of the study does not exempt the clinician from the obligation to report any material vigilance in accordance with the legislation in force (L.52-12 and R5212-14).

5 *Logistical aspects*

5.1 Conduct of the study

Launch of the study

This phase includes:

- Information from the centers to present the study and its modalities;
- The printing of the questionnaires;
- The implant of procedures for monitoring the study;
- The development of the necessary tools: database for data entry;

The centers will be informed of the study by Boston-Scientific technicians, who will also provide the study documents.

Centers will be informed of the data to be collected for pain assessment, so that the proposed tools are systematically used in the indication phase of a pacemaker implantation (before the test) and the necessary data are actually available at the time of patient inclusion (implantation).

Inclusion data collection

The data will be collected by the investigators in the questionnaires that will have been given to them and explained during the implant by the technicians. The questionnaires of the same patient will be grouped into a file that can be placed in the patient's medical file, so that the clinician will consider completing the follow-up questionnaires. These study records will be pre-numbered with the center number and patient number to facilitate longitudinal follow-up and ensure that questionnaires for the same patient are matched correctly. Each patient will be identified by their initials, so as to avoid errors.

Questionnaires and follow-up sheets will be duplicated so that the clinician keeps a duplicate in the patient's file included.

Collection of monitoring data

Data will be collected between 1 to 3 months after implantation, at 6 months, 1 year and 2 years. For patients not seen during the period, clinicians will be contacted and will be able to specify the date of the latest news.

At the end of the 1st and 2nd year of follow-up, a report per center and per patient will be prepared and the centers will be relaunched for patients who have no follow-up form during the year.

Telephone reminders from the centers will also be used to validate or complete data collected in the monitoring sheets.

Patient self-questionnaires

Much of the information on pain, its impact and treatment will be collected directly from the patient through a patient self-questionnaire to be completed at inclusion and at each follow-up point.

This questionnaire will include the measurement of pain on the digital scale, the impact of pain on activities of daily living, the measurement of quality of life (SF12), the measurement of anxiety and depression and treatment consumption. In the follow-up questionnaires, there will also be two questions on the perception of pain progression in relation to before implantation and in relation to the previous visit.

The self-inclusion questionnaire will be completed by patients before the test phase for primary implants and before the reimplantation of the new device for the others. This questionnaire will then be returned by the investigator with the inclusion medical questionnaire, once the patient is definitively included.

Follow-up self-questionnaires will be completed by patients at the time of follow-up consultations and returned by the clinician along with the self-questionnaire component.

5.2 Monitoring and data management

Identification of files

Patients will be identified by a number consisting of a center number (2 digits) and a patient number (3 digits). All data will be entered and analysed by Cemka-Eval. The personal data necessary for the follow-up of patients not seen in the centers will not be entered into the database, but only used from the questionnaires to telephone the patient or his or her attending physician.

Monitoring data quality

Cemka-Eval will be responsible for monitoring, quality control, sending requests for corrections, data entry and analysis.

Additional information requests will be made to participating physicians for missing or inconsistent information based on the data validation plan. Contacts will be made by mail, e-mail or telephone according to the method best suited to each doctor and each situation. It should be noted that in case of difficulties in obtaining follow-up data, the study monitor will contact the investigating physician and, if necessary, consider an on-site visit.

For patients not seen at 1 and/or 2 years by the investigating physicians, there is provision for telephone contact with the patient or his or her treating physician in order to collect minimum information on the patient's situation (vital status, device still in place or not).

Follow-up assessments

Monitoring will include monthly reviews of inclusions and returns of monitoring forms, as well as monitoring calls. A newsletter will be published every month to allow the centers to follow the study regularly.

Treatment of adverse events

All adverse events will be systematically analysed by the Cemka-Eval project manager upon receipt. Events likely to be related to the device as well as deaths will have been reported to Boston Scientific by the Boston Scientific Center representative in accordance with Boston Scientific's Quality/Regulatory Affairs procedure. Upon receipt of the above-mentioned event forms, if it is mentioned that the Boston Scientific representative has not been informed by the center, Cemka-Eval will inform him as soon as possible and within a maximum of three (3) calendar days.

The events will also be reviewed as a whole at a meeting of the Scientific Committee, which will decide for each event whether or not it can be attributed to the system.

5.3 Study schedule

Table 2: Projected study schedule

	2011-2012	2013		2014		2015		2016	
		1st semester	2nd semester	1st semester	2nd semester	1st semester	2nd semester	1st semester	2nd semester
Preparatory phase									
Data collection									
Inclusion / Implant									
1 year follow-up									
2-year follow-up									
Analysis and reporting									
Inclusion									
1 year follow-up									
2-year follow-up									

6 *Analyses and reports*

6.1 *Analyses*

The statistical analysis will be carried out by Cemka-Eval using SAS V9.2 software (SAS Institute; North Carolina).

For each of the qualitative variables analyzed in the different phases, the analysis will present the number of missing responses, the number and percentage in each category and its 95% confidence interval.

For each of the quantitative variables analyzed at the different phases, the analysis will present the number of missing responses, the number of employees, the mean and standard deviation, the median, the minimum and the maximum.

Comparisons will be made using Chi-2 tests, exact Fisher tests, t-tests or non-parametric tests and analysis of variance.

Sub-population analyses (primary implantation vs. replacement of implantation) will be carried out.

Description of the centers

The participating centers will be described according to the following characteristics:

- Public/private status;
- The level of activity;
- The specialty of the physicians who participate in the consultation meeting and who practice implantations;
- The method(s) of implantation practiced;
- Patient follow-up practice (collected at the time of implant visits).

The sample of centers will be compared to all centers performing these treatments.

Data at the time of implant

The analysis of the data at the time of implantation will aim to describe the patients implanted, according to the diagnosis (type and cause of pain). In particular, it will make it possible to compare the characteristics of the patients implanted with the indications retained in the CNEDIMTS opinion. Information outside the scope of the selected information will be described in detail. The type of equipment implanted and the modalities of implant will also be described. The complications likely to occur at the time of implantation or at its immediate onset will be quantified and described.

The simple descriptive analysis will be performed to describe:

- The characteristics of patients and their disease at the time of implantation: type of pain and impact of pain on daily living activities and quality of life;
- Previous treatments;
- The implantation modalities (identification, implantation of the electrodes and the stimulator);

- Early complications (during implantation and the first month of follow-up).

With regard to complications, death and complications requiring hospitalization will be analysed in particular. All complications will be described in terms of hospitalization consequences, reversibility and possible link to treatment.

For pain and quality of life data, the analysis will include a description of pain levels and quality of life.

Data from the non-inclusion registers will also be analysed in order to assess the completeness of inclusions in relation to the activity over the period in the participating centers and to describe the reasons for non-inclusion.

Early follow-up data (1 to 3 months), 6 months and 1 year and 2 years

The analysis of early and long-term follow-up data (1 year, 2 years) will make it possible to document the long-term benefit of spinal cord stimulation on the level of pain by calculating the percentage change in pain scores on the numerical scale compared to the previous state and the change in other parameters (impact on activities of daily living, quality of life, change in consumption of other pain treatments).

The primary endpoint will be determined as the percentage of primary implanted patients with an improvement of 50% or more, but the distribution of patients in terms of pain progression and pain level will also be described at each phase. The calculation will be based on the difference in the usual pain level over the last 8 days, compared to the initial level. The 30% improvement threshold will also be taken into account as a secondary judgment criterion. These criteria for improving pain intensity may be weighed against secondary judgment criteria (patient judgment, changes in impact on activities of daily living and quality of life, changes in drug use).

The evolution of drug consumption will be analyzed in relation to pre-implantation treatment. The evolution of drug consumption will be quantified for morphine treatments and will indicate the percentages of patients with an increase, stability, decrease or discontinuation of treatment for the different treatment modalities.

Short- and medium-term complications will also be quantified and described, in the same way as for implantation. Mortality and morbidity will be described.

Comparative analyses will be carried out:

- Depending on the consumption of analgesic or non-analgesic drugs during the use of the neurostimulator;
- The indication that the neurostimulator has been placed in a primary or secondary implantation.

On follow-up data, at each phase of analysis, survival analyses will document survival, device maintenance, taking into account patient follow-up times. In the event that there are missing data for the 1-year follow-up and then 2-year follow-up data for some patients, analyses using mixed models may be used to take into account all patients and the data collected.

In the event of missing data or patient lost to follow-up, the variables for the evaluation criteria will be replaced for the main analysis by a **multiple imputation** method. Sensitivity analyses will be carried out.

Adverse event analysis

Adverse events will be classified according to ISO14155 criteria as follows:

- **Adverse Effect (AE)** (ISO14155:2011 3.1) :

Adverse event related to the use of the medical device under study.

Note 1: This definition includes adverse events resulting from a deficiency or defect in an instruction manual, during deployment, implantation, installation, operation or any malfunction of the medical device under study.

Note 2: This definition includes any event resulting from an error in the use or intentional misuse of the medical device under study.

- **Serious adverse event (SAE)** (ISO 14155:2011 3.37) :

Undesirable event that:

a) results in death,

(b) results in a serious deterioration in the health status of a patient resulting from:

(1) a life-threatening disease or condition,

2) or in a permanent impairment of a structure/function of his body,

3) either in a new hospitalization or in an extension of hospitalization,

4) or in a medical or surgical intervention to prevent permanent damage to a structure/function of his body;

(c) results in fetal distress or death, congenital anomaly or birth defect.

Note: A scheduled hospitalization for an existing condition or procedure required by the Clinical Investigation Plan, without a serious deterioration in health status, is not considered a serious adverse event.

6.2 Reports

Three reports will be written:

- the first on the inclusion data;
- the second at the end of the 1-year follow-up;
- the final report will be written at the end of the 2nd year of monitoring.

The reports will include a presentation of the method and conduct of the study, as well as all the available results.

6.3 Communication and publication

The study will potentially be published in a peer-reviewed scientific journal.

To maintain the support of the centers, a summary of the results in the form of an information letter during the inclusion and interim reports will be sent to them by e-mail. This letter will present the results obtained and provide advice for the successful collection of monitoring data.

7 *Bias and limits*

7.1 Representativeness of the sample of investigators and patients

Provided that the inclusions and follow-up data are complete, this study should describe current practices for the use and outcomes of PRECISION® neurostimulation in the treatment of chronic rebellious pain in current practice.

Limitations are the potential difficulties in ensuring completeness and harmonizing monitoring practices in a pragmatic study, particularly for monitoring tools. Indeed, the HAS opinion specifies the framework for the use of these devices, in terms of user centers, implanter characteristics, validation of the indication, stimulation test showing a pain improvement of at least 50%, and the need for long-term follow-up. However, it does not specify the tools to be used in current practice for pain assessment before implantation and throughout follow-up.

However, it will not be possible to control the selection bias associated with possible refusals of participation by doctors in some centers. In order to measure this potential bias, an analysis of the characteristics of participating and non-participating centers (if any) will be conducted.

In addition, a non-inclusion register will describe situations where patients who meet the inclusion criteria have not been included by the investigators.

7.2 Difficulties in patient follow-up

The duration of the study follow-up will be 2 years, with a proposed follow-up data collection every year, but not required due to the observational nature of the study. There is a risk that some patients may be lost to follow-up. This risk is estimated at about 10% per year of follow-up.

Throughout the study, actions will be implemented to minimize the rate of vision loss. They include:

- Information for investigators on the conduct of the study (newsletters, personalized letters);
- Customized reminders based on sales information
- Follow-up to improve the quality of the data collected
- Follow-up to collect follow-up questionnaires

It is also provided that in the event of difficulties in obtaining follow-up data from the investigator or for patients not seen in the center that included them, the study monitor may contact the patient himself or his attending physician.

These measures may be adapted during the course of the study according to the rate of loss of sight observed, in particular by deciding to carry out monitoring visits in certain centers.

A comparative analysis will be made between patients followed over the 2 years and those lost to follow-up. This will make it possible to identify possible biases affecting the duration of follow-up in the study. Some missing data will be imputed during the analysis and sensitivity analyses will be performed.

7.3 No control cohort

This study is an observational study and therefore has the inherent limitations of this type of study. Since the objectives of this study are to describe patients treated with PRECISION® in real-life treatment situations, no comparator group is included in the protocol. Thus, the comparison with data concerning patients treated with treatments other than PRECISION® will not be carried out. However, it may be considered to compare the results obtained in this observational study with those obtained in clinical studies conducted with the different neurostimulators used in the treatment of chronic rebellious pain.

8 *Regulatory aspects*

8.1 Sponsor of the study

The promoter of the study is CEMKA-EVAL.

8.2 Study funder

The study is funded by Boston-Scientific International.

8.3 Scientific Committee

This study will be designed and conducted with the help of a Scientific Committee (SC) composed of the following experts:

- Professor Jean-Paul NGUYEN, Neurosurgeon, Neurosurgery Department, René Laënnec Hospital, Nantes University Hospital
- Professor Patrick MERTENS, Neurosurgeon, Weirtheimer Neurological Hospital, Bron
- Dr. Etienne LAJOUS, anaesthetist, Clinique du Parc, Toulouse
- Doctor Jean LEMARIE, anaesthetist, Clinique St Léonard, Angers
- Dr Michel LANTERI-MINET, Neurologist, Pasteur Hospital, Nice

Its role is to:

- Participate in methodological discussions;
- Validate the study documents (protocol, observation book, self-questionnaires);
- Propose the necessary amendments;
- Decide on an external audit, if necessary;
- Validate the statistical analysis plan;
- Validate the inclusion report, the 1-year follow-up report and the final report;
- Define publication rules and final signatures;
- Communicate results at the global level.

8.4 Administrative declarations

Agreement of participating physicians

This protocol will be presented to prospective physicians before asking them to confirm their participation. This will be confirmed by signing a participation form.

In accordance with article R.5120 of the Public Health Code, doctors and all persons called upon to collaborate in the study are bound by professional secrecy with regard to the methods of carrying out the study, the persons who lend themselves to it and the results obtained. They may not, without the consent of the sponsor, give information relating to the study to persons not belonging to the Health Authorities.

Declaration to the National Council of the Order of Physicians (CNOM)

Cemka-Eval on behalf of Boston Scientific will submit the investigators' financial contract to the National Council of the Order of Physicians for its opinion.

Statements to the Consultative Committee on the Processing of Information in the Field of Health Research (CCTIRS) and to the National Commission on Informatics and Liberties (CNIL)

This study, which requires the collection of personal health data for the purpose of health research, is covered by Chapter IX of the amended French Data Protection Act of 6 January 1978. It must be the subject of a request for an opinion from the Advisory Committee on the Processing of Information on Health Research (CCTIRS), and an application for authorisation from the Commission Nationale Informatique et Libertés (CNIL).

The use of indirectly nominative data (identification of patients using a center and patient number) is justified by the need to be able to make requests for additional information from participating doctors after receipt and entry of the questionnaires, in order to guarantee the quality of the data, and to be able to carry out a control in the event of a dispute during the computerisation of the data.

The first page of the observation booklet contains personal data (date and commune of birth of the patient, telephone number and contact details of the attending physician). This data will not be entered and will only be used if the patient is lost to follow-up before the end of the study. This page will therefore be detached from the questionnaire by the CRA of Cemka-Eval before the notebooks are entered. If the patient, the attending physician or the commune of birth must be called because the patient has been lost to the investigator, the data collected by telephone will be anonymized: they will only be identified by the center number and the patient number. The call database will also not contain any personal data.

In accordance with the amended "Informatique et Libertés" law of 6 January 1978, the patient will be informed of his right of access, opposition and rectification of the data recorded during this study, this right may be exercised at any time with his doctor.

Nominative information relating to participating physicians will be declared and physicians will be informed of their right of access, opposition and rectification of this information as part of their financial agreement.

Patient document

In accordance with the "Informatique et Liberté" law, the patient will be informed in writing of the nature and purpose of the study, as well as his or her right of access, opposition and rectification of the data recorded during the study. He will sign this information note.

8.5 Material vigilance and post-marketing surveillance

All the devices used in this study are CE marked. Therefore, post-market surveillance is applicable. It is the investigator's responsibility to report all complaints and product malfunctions immediately through the usual channels for CE marked products.

For an observational study, the standard material vigilance procedure applies, i.e. the clinician must complete the CERFA material vigilance form (presented in Appendix 1 and available in the investigator's administrative folder) for all events related to the device or in the event of death and send it to Boston-Scientific and ANSM within 3 days of the day on which the event was brought to his attention.

8.6 Recommendation of good practices


The study will follow the recommendations of the Association des Epidémiologistes de Langue Française (^{vii}ADELFF), good clinical practices and the HAS Methodological Guide on post-inscription studies on health technologies (drugs, medical devices and procedures)^{viii} for both data collection and processing.

8.7 Archiving

Study data collection forms will be archived in paper form by Boston Scientific for a minimum of 15 years.

Appendices


8.8 Appendix 1. Cerfa form (N°10246*04)



Agence nationale de sécurité du médicament
et des produits de santé


143/147, bd Anatole France
93285 Saint-Denis Cedex
Fax : 01 55 87 37 02

ENVOI PAR FAX :
Si un accusé de réception ne vous est pas
parvenu dans les 10 j, prière de confirmer le
signalement par ENVOI POSTAL AVEC A.R.



**SIGNALEMENT
D'UN
INCIDENT ou
RISQUE D'INCIDENT**

Code de la Santé publique : articles L. 5212-2,
R. 5212-14 à 16



N° 10246*04

Cadre réservé à l'ANSM

Numéro

Attributaire

Sous-commission

Date d'attribution

Date d'envoi du signalement

L'émetteur du signalement		Le dispositif médical impliqué (D M)	
Nom, prénom		Dénomination commune du D M	
Qualité		Dénomination commerciale: modèle/ type/ référence	
Adresse professionnelle		N° de série ou de lot	Version logicielle
code postal commune		Nom et adresse du fournisseur	
E-mail		code postal commune	
Téléphone		Nom et adresse du fabricant	
Fax			
<input type="checkbox"/> Etablissement de santé : N° FINESS <input type="checkbox"/> Association distribuant DM à domicile		<input type="checkbox"/> Fabricant / Fournisseur <input type="checkbox"/> Autre	
L'émetteur du signalement est-il le correspondant matériovigilance ? <input type="checkbox"/> Oui <input type="checkbox"/> Non		code postal commune	
L'incident ou le risque d'incident			
Date de survenue	Lieu de survenue		
Si nécessaire : nom, qualité, téléphone, fax de l'utilisateur à contacter			
Circonstances de survenue / Description des faits		Conséquences cliniques constatées	
Le cas échéant joindre une description plus complète sur papier libre. Préciser alors le nombre de pages jointes, <input type="text"/> et rappeler le nom de l'émetteur sur chaque page.		Mesures conservatoires et actions entreprises	
Situation de signalement (de A à N) <input type="text"/> voir nomenclature page 2/2		Le fabricant ou fournisseur est-il informé de l'incident ou risque d'incident ? <input type="checkbox"/> Oui <input type="checkbox"/> Non	

La loi n° 78-17 du 6 janvier 1978 relative aux fichiers nominatifs garantit un droit d'accès et de rectification des données auprès de l'organisme destinataire du formulaire (l'ANSM).

Appendix 2. References

- ⁱ Burchiel KJ, Anderson VC, Brown FD. Prospective Multicenter Study of Spinal Cord Stimulation for Relief of Chronic Back and Extremity Pain. *Spine*. 1996; 21:2786-94.
- ⁱⁱ Kumar K, Toth C, Nath RK and Lain P. Epidural spinal cord stimulation for treatment of chronic pain-some predictors of success. *Surg Neurol* 1998;50:110-121.
- ⁱⁱⁱ North RB, Kidd DH, Zahurak M, et al: Spinal cord stimulation for chronic, intractable pain: Experience over two decades. *Neurosurgery* 1993;32:384-394.
- ^{iv} Segal R, Stacey BR, Rudy TE, Baser S, Markham J. [Spinal cord stimulation revisited](#). *Neurol Res*. 1998;20(5):391-6.
- ^v J.C. Oakley et al. Successful long-term outcomes of spinal cord stimulation despite limited pain relief during temporary trialing. *Neuromodulation: Technology at the Neural Interface*, 2008, Vol.11, Nb.1, 66:73.
- ^{vi} Bouhassira D, Attal N, Fermanian J et al. Development and validation of the Neuropathic Pain Symptom Inventory. *Pain* 2004 ; 108 (3) : 248-57.
- ^{vii} Ethics and good practices in epidemiology. 1998 updated in 2008. Available on the website: <http://adelf.isped.u-bordeaux2.fr/>
- ^{viii} Methodological guide. Post-registration studies on health technologies (drugs, medical devices and procedures). HAS, November 2011.
http://www.has-sante.fr/portail/jcms/c_1191960/les-etudes-post-inscription-on-health-technologies-drugs-medical-devices-and-actes?xtmc=&xtcr=1